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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte GEORGE C. TSOKOS and YUANG-TAUNG JUANG

Appeal 2010-003183
Application 10/772,704
Technology Center 1600

Before TONI R. SCHEINER, LORA M. GREEN and FRANCISCO C. PRATS, Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 1, 10, 11, 15, 29, and 30, directed to a method of increasing IL-2 production in T cells of a patient with systemic lupus erythematosus. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

STATEMENT OF THE CASE

Appellants have not presented separate arguments for the claims, therefore, we select claim 1 as representative of the claimed subject matter. 37 C.F.R § 41.37(c)(1)(vii):

1. A method of increasing IL-2 production in systemic lupus erythematosus T cells in a patient that has systemic lupus erythematosus comprising:

administering gene-modified T cells to said patient, said T cells originating from said patient and having been gene modified by treating them with antisense cAMP response element modulator (CREM) plasmid thereby increasing the expression of IL-2 in said T cells in said patient.

The Examiner rejected claims 1, 10, 11, 15, 29, and 30, all the claims pending, under 35 U.S.C. § 103(a) as unpatentable over Solomou,[1] Weintraub,[2] Monia,[3] Symonds,[4] and Gruenberg.[5]

We affirm.

ISSUE

The Examiner finds that Solomou teaches that IL-2 is a growth factor for T lymphocytes, and is exclusively provided by T cells, and further teaches that T cells from SLE patients produce decreased amounts of IL-2 as a result of gene transcriptional repression mediated by the binding of CREM, a strong repressor of IL-2 production (Ans. 4). According to the

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[1] Elena E. Solomou et al., Molecular Basis of Deficient IL-2 Production in T Cells from Patients with Systemic Lupus Erythematosus, 166 J. IMMUNOL. 4216-4222 (2001).
[2] Harold M. Weintraub, Antisense RNA and DNA, SCIENTIFIC AMERICAN 40-46 (1990).
[3] US 6,159,697, Monia et al., issued December 12, 2000.
[4] US 7,345,025 B2, Symonds et al., issued March 18, 2008.
[5] US 2003/0134415 A1, Gruenberg, July 17, 2003.

Examiner, "[a] person of ordinary skill in the art . . . would have recognized the desirability of increasing IL-2 production by inhibition of the suppressor protein CREM in SLE patients" (id. at 5). The Examiner concludes that it would have been obvious to use ex vivo antisense technology to inhibit expression of CREM in T cells of SLE patients using the techniques described by Weintraub, Monia, Symonds, and Gruenberg (id. at 4-6).

Appellants contend that Solomou represents "very early work" (App. Br. 5), "leaves a lot to speculation" (Reply Br. 2), and does not "conclude that CREM alone is responsible for decreased IL-2 production in SLE patients" (App. Br. 5). Appellants contend, moreover, that the additional references cited by the Examiner would not have motivated one of ordinary skill in the art to use antisense technology to inhibit expression of CREM as a means of increasing IL-2 production (id. at 6-10).

The issue raised by this appeal is whether Solomou would have suggested increasing IL-2 production in T cells from SLE patients by inhibiting expression of CREM, and moreover, whether it would have been obvious to inhibit expression of CREM using antisense technology.

FACT FINDINGS

The following fact findings are supported by a preponderance of the evidence of record:

1. Solomou teaches that systemic lupus erythematosus (SLE) "is a multifactorial autoimmune disease characterized by diverse cellular and biochemical aberrations, including decreased production of IL-2" (Solomou, Abstract), resulting in defective regulation of B cell Ig production, which has a number of consequences and ultimately leads to inflammation, organ failure, and life-threatening infections (id. at 4216, col. 1).

2. In normal T cells, "IL-2 gene expression is regulated by the cooperative binding of discrete transcription factors [AP-1, NF-AT, and NF-κB] on the IL-2 promoter/enhancer and is predominantly controlled at the transcriptional level" (Solomou 4216, cols. 1-2).

3. In T cells of SLE patients, however, binding of AP-1 is not detectable (Solomou 4217, col. 2), and "decreased production of IL-2 is the result of active IL-2 gene transcriptional repression mediated by the binding of phosphorylated CREM (p-CREM) to the -180 site of the IL-2 promoter" (id. at 4216, col. 2). Moreover, binding of p-CREM is not detectable in normal T cells (id. at 4217, col. 2).

4. Solomou concludes that "p-CREM acts as a repressor of the IL-2 promoter in SLE T cells" (Solomou 4222), and suggests that "[i]t is possible that decreased IL-2 production by SLE T cells reflects an integrated effect of diminished activators (e.g., NF-κB) and excessive expression of repressors (e.g., p-CREM)" (Solomou 4221, col. 2).

5. Weintraub teaches that antisense RNA can turn off endogenous cellular genes, e.g., the gene encoding actin in vertebrate cells; the fos, ras, and cis genes in transformed cells; and the gene encoding cyclin (Weintraub 43, col. 2; 45, col. 2).

6. Monia is directed to antisense compositions and methods for modulating the expression of a particular human transcription factor, Smad7, and also discusses antisense techniques and compositions generally (Monia, col. 3-6).

7. Symonds discusses ex vivo gene therapy involving removing hematopoietic stem cells from a patient, introducing a gene into the stem

cells, e.g., a gene directing the synthesis of antisense RNA, and reintroducing the cells to the patient (Symonds, cols. 13-14).

8. Gruenberg discloses an immunotherapy technique for treating various diseases, including cancer and SLE (Gruenberg ¶¶ 13-14). The method involves the steps of: "(i) collecting source material from a subject; (ii) purifying T-cells from the source material; (iii) activating frequently . . . and repeatedly . . . the purified T-cells; and optionally (iv) reinfusing the resulting cells into the same subject or an allogenic recipient" (id. at ¶ 15).

DISCUSSION

We agree with the Examiner that the prior art reasonably suggests the desirability of increasing IL-2 production by inhibiting expression of the repressor protein CREM in the T cells of SLE patients, given the fact that Solomou teaches that decreased production of IL-2 in SLE is the result of selective, active transcriptional repression mediated by the binding of phosphorylated CREM (p-CREM) to the -180 site of the IL-2 promoter in SLE T cells (FF3). Moreover, we agree with the Examiner that it would have been obvious to use ex vivo antisense technology to inhibit expression of CREM in T cells of SLE patients, given (a) the fact that Weintraub and Monia teach that antisense RNA can inhibit expression of targeted genes in a wide range of cell types, including endogenous genes in vertebrate cells (FF5, FF6); (b) the fact that ex vivo therapy involving introducing a gene into a patient's cells, (e.g., a gene directing the synthesis of antisense RNA), and reintroducing the cells to the patient was disclosed in the art (FF7); and (c) the fact that techniques for removing a cell sample from a patient, purifying T cells from the sample, manipulating the T cells ex vivo, and reintroducing them into the patient were available (FF8).

We are not persuaded otherwise by Appellants' argument that Solomou "was very early work" (App. Br. 5), "CREM and CREB are normal compounds found in humans" (id.), and "much was unknown about the pathways of CREM binding in Lupus patients" (id.), "why CREM bound to the IL-2 promoter in Lupus patient's T-cells" (id.), or "how to stop CREM from binding to the IL-2 promoter" (id.). Nor are we persuaded by the argument that "[n]one of the cited references . . . conclude that CREM alone is responsible for decreased IL-2 production in SLE patients" (id.), and "one of ordinary skill in the art . . . would have understood that multiple transcriptional factors could be the problem" and "the solution could be found in addressing the mechanisms that lead to increased pCREM . . . and a discovery of other positive transcription factors that bind to the IL-2 promoter" (id. at 6).

Solomou unambiguously identifies CREM binding to the IL-2 promoter in the T cells of SLE patients as a significant factor in decreased IL-2 production in SLE patients (FF3, FF4), and further notes that CREM binding is not detectable in normal T cells (FF3). It is certainly true that Solomou teaches that decreased IL-2 production by SLE T cells may be due to an integrated effect of excessive expression of the repressor CREM, together with diminished activator binding (FF4). Nevertheless, Appellants have not explained why one of skill in the art, even without knowing why CREM selectively binds to the IL-2 promoter in SLE T cells, would not have wanted to inhibit CREM as part of a comprehensive approach to increasing IL-2 production in SLE T cells - especially as CREM binding is not detectable in normal T cells (FF3). In any case, nothing in the present

claims precludes modulating positive transcription factors in addition to the repressor.

As for how one would attempt to stop CREM from binding to the IL-2 promoter, we are not persuaded by Appellants' argument that Weintraub "only speculates that viral diseases or dangerously mutated oncogenes might be treated" using antisense technology, and "does not suggest that diseases wherein defective genes are present in lymphocytes or other naturally occurring cells of the human body could be treated" using antisense technology (App. Br. 6-7).[6] Appellants' characterization of Weintraub's teachings is unduly narrow. As discussed above, Weintraub teaches that antisense technology can be used to turn off endogenous cellular genes, e.g., the gene encoding actin, a ubiquitous protein in vertebrate cells (FF5). Appellants have not explained why one skilled in the art would not expect antisense technology to be equally effective in inhibiting the gene encoding CREM.

In addition, Appellants contend that Monia doesn't disclose or suggest that antisense modulation would have any effect on IL-2 production in Solomou's T cells, or that "administering gene-modified T cells treated with antisense cAMP response element modulator plasmid would actually increase the production of IL-2 in patients with SLE" (App. Br. 9).

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[6] Appellants reproduce isolated excerpts from several references on pages 7-8 of their Appeal Brief in support of their contention that "the literature at the time and available to one of ordinary skill actually taught against" using antisense technology. Appellants have not explained the relevance of these references to ex vivo use of antisense compounds, nor have the underlying references been made of record. Accordingly, we will not address them further.

Similarly, Appellants contend that Symonds "is not directed to the claimed highly complex immunological T cells" and "did not solve the mystery of why CREM is increased in SLE T cells or whether there were other transcriptional factors that effect IL-2 production or why CREM production decreased in SLE patients following stimulation" (id.). Finally, Appellants contend that Gruenberg's approach "is very different than the present invention" (id. at 10), which corrects the T-cells not just activates them" (id.), and "[m]ore importantly, does not overcome Symonds, Monia, and Weintraub[']s lack of teaching that CREM is the only reason that IL-2 production is decreased in SLE patients" (id.).

Appellants' arguments are not persuasive. As discussed above, the concept that CREM binding to the IL-2 promoter in the T cells of SLE patients is a significant factor in decreased IL-2 production in SLE patients, and that decreased IL-2 production by SLE T cells is due, in significant part, to excessive expression of CREM, comes from Solomou. The Weintraub, Monia, Symonds, and Gruenberg references were not cited to confirm or expand Solomou's conclusions regarding the relationship between excessive expression of CREM and decreased IL-2 production, but simply to show that ex vivo antisense techniques for modulating protein expression were known, as were specific techniques for isolating T cells from a patient, manipulating the cells, and reintroducing them.

CONCLUSION

The evidence of record is sufficient to support the Examiner's conclusion that Solomou would have suggested increasing IL-2 production in T cells from SLE patients by inhibiting expression of CREM, and that it would have been obvious to inhibit expression of CREM in cells isolated from SLE patients using antisense technology.

SUMMARY

We affirm the rejection of claims 1, 10, 11, 15, 29, and 30 under 35 U.S.C. § 103(a) as unpatentable over Solomou, Weintraub, Monia, Symonds, and Gruenberg.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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